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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,854	06/12/2001	Raymond F. Schinazi	18085.105093	3686

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EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/879,854	SCHINAZI ET AL.	
	Examiner	Art Unit	
	Traviss C. McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-20* is/are pending in the application.

4a) Of the above claim(s) *5,6,8-13,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,7,14 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Species 1, purine nucleosides in the reply filed on October 20, 2003 is acknowledged.

Claims 5-6, 8-13, and 15-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 20, 2003.

An action on the merits of the portion of claims 2-4, 7, 14, and 17-20 which are drawn to the use of purine compounds is contained herein below.

Specification

The disclosure is objected to because of the following informalities:

On page 8, in the description of the figures, the specification states that "figure 1 is an illustration of the chemical structures of β-L-FddC, β-D-ddC, β-L-ddC, β-L-FTC, β-D-FDOC, and β-L-2-amino-6-(R^4)-9-[(4-hydroxymethyl)-tetrahydrofuran-1-yl]purine". However, it is noted that figure 1 does not comprise the structure for β-L-2-amino-6-(R^4)-9-[(4-hydroxymethyl)-tetrahydrofuran-1-yl]purine as stated on page 8.

The tables on pages 33 and 36 are both labeled "Table 1".

Example 4 on page 35 refers to "Table 4", which is not present in the instant application.

Example 5 on page 37 refers to "Table 5", which is not present in the instant application.

It is noted that this is not intended to be an inclusive list of all the minor errors that may be present in the instant application, and applicants are encouraged to review the specification and make any corrections as deemed necessary, but also to be mindful not to introduce any new matter.

Appropriate correction is required.

Claim Objections

Claim 2 is objected to because of the following informalities: the claim has the beginning of the parenthesis typed in twice in defining the second compound b) as "2',3'-dideoxyinosine ((DDI)". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-4, 7, 14, and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue

experimentation. Applicants are not enabled for the methods of using the combinations as instantly claimed.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

Claim 2 is drawn to a method of treating a patient infected with HBV and HIV comprising administering to the patient a combination of 2 compounds, one being a 2',3'-dideoxypurine and another being one of AZT, DDI, D4T, FTC, a non-nucleoside RT-inhibitor, or a salt or prodrug thereof. Claim 3 provides the first compound is in enantiomerically enriched form. Claim 4 limits the first compound to that of structure I. Claim 7 limits the first compound to that of structure IV. Claim 14 provides the 1st compound is β-L-2-amino-6-(OH, Cl, NH_2, or H)-9-[(4-hydroxymethyl)-tetrahydrofuran-1-yl]purine or a salt or prodrug thereof. Claim 17

provides the first compound is β-L-2',3'-dideoxyadenosine. Claim 18 provides that the β-L-DDA of claim 17 is in enantiomerically enriched form. Claim 19 provides the first compound is that of structure VII. Claim 20 provides that structure VII of claim 19 is in enantiomerically enriched form. It is noted that the number of various combination encompassed by the instant claims is likely to be in the thousands, especially since one of the active agents which is optionally included therein is described by it's function, rather than it's chemical name (i.e., a non-nucleoside RT-inhibitor).

The state of the prior art

HBV and HIV are both known to be viral infections which can be treated with β-L-nucleosides (WO92/18517). The biologically active form of many nucleosides is the triphosphate form, which inhibits DNA polymerase or reverse transcriptase or cause chain termination. However, the nucleoside derivatives used to treat HBV or HIV are normally administered in the unphosphorylated form (as nucleosides) as the triphosphate form has typically been dephosphorylated before reaching the cell or is poorly absorbed by the cell. Nucleotides in general are known to generally cross cell membranes very inefficiently and are generally not very potent in vitro. Regarding combination therapy, drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished

effects of one or both of the drugs, or the appearance of new effects which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of a given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56.

The level of predictability in the art

As seen by Goodman & Gilman, the art of combination therapy is unpredictable. Drug-drug interactions are known to be beneficial or adverse, yet there is no way to know until the drugs are actually tested in an individual.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed

method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the claims as written. Applicants have not provided any indication of what drugs might be toxic and what the drugs therapeutic indexes are. Applicants have not provided any structural requirements for "non-nucleoside RT-inhibitors", and these could be any of various compounds having diverse structure and functional groups available for reactions.

The existence of working examples

There are no examples using combination therapy. There are no compositions made with multiple agents.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable one to make or use the combination of the various purine moieties and any of the other agents without undue experimentation. It is noted that the specification should teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. See ***In re Gardner, 166 USPQ 138 (CCPA 1970).*** In order to practice the instant invention, one of ordinary skill in the art would be confronted with the undue burden to optionally first determine if a drug actually performed the functionally described activity of being a non-nucleoside RT-inhibitor. If the skilled artisan did determine if the drug had the activity, then they would be required to determine whether the drug would interact with the purine derivative, first *in vitro*, and then *in vivo*. Also, they would also have to make the other alternative combinations of the various purine derivatives and each of the various agents a-d and subsequently determine if the drugs interacted with each other both *in* vitro, then *in* vivo. And if

the drug did interact, the artisan would be required to determine how they interacted, did the interaction provide adverse effects or beneficial effects, or produce completely new effects? They would be required to determine at what point in the patients system the effect occurred, and determine what is needed to ensure the patient was effectively treated. One of skill in the art would not be able to use the invention as instantly claimed without undue experimentation as the art recognizes the unpredictability of drug-drug interactions.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C. McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 20, 2006

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